Long-term safety evaluation of placental mesenchymal stromal cells for in utero repair of myelomeningocele in a novel ovine model.

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Public Summary:
Myelomeningocele (MMC), the most severe form of spina bifida (SB), is a birth defect characterized by the incomplete closure of the neural tube early during pregnancy. This congenital injury results in the spinal cord being exposed to the intrauterine environment for the remainder of the pregnancy, leading to accumulated damage to the exposed spinal cord. The current standard of care for MMC is fetal surgery to close the defect, but clinical manifestations of predominantly lower extremity lifelong paralysis persist. Our group aims to augment the current standard of care by applying clinical-grade placental-derived mesenchymal stem cells (PMSCs), seeded on an FDA approved extracellular matrix (ECM) patch, directly to the spinal cord at the time of the standard of care fetal surgery in the gold-standard fetal sheep model of MMC. The clinical-grade PMSC-ECM patch was prepared at a Good Manufacturing Practice (GMP) Facility, as required by the FDA, as well as all relevant cell work. We assessed long-term safety of the clinical-grade human PMSC-ECM treatment in a sheep animal model, in preparation for a human clinical trial. The goal of this study was to assess long-term safety, and not efficacy, of the PMSC-ECM product. As such, we created a revised surgical model of MMC for this study, which allowed for the direct application of the PMSC-ECM product to the spinal cord, without injury to the spinal cord that would create the associated clinical manifestations of MMC, such as hind limb paralysis. We hypothesized that the application of the PMSC-ECM product directly onto the spinal cord at the time of fetal surgery would not cause any tumor formation in the lamb and that the PMSCs would no longer be present after 3 months. There were 5 lambs that received surgical intervention and 6 control lambs that received no surgical intervention. Results showed no visible evidence of a mass in any of the surgical intervention lambs that received the PMSC-ECM treatment or their moms, no evidence of seizures and no deaths. We found no evidence of abnormal tumor growth and no evidence of the spinal cord tethering to the PMSC-ECM patch on MRI scans. We found no evidence of abnormal tumor growth during histological analysis of the tissues from the lambs or the uteri of the moms. We found no human DNA in the evaluated tissues, which indicates the absence of human PMSCs. These results indicate that the PMSC-ECM patch is safe to use and can proceed to human clinical trials to evaluate the PMSC-ECM product for fetal MMC repair.

Scientific Abstract:
PURPOSE: Augmentation of in utero myelomeningocele repair with human placental mesenchymal stromal cells seeded onto extracellular matrix (PMSC-ECM) improves motor outcomes in an ovine myelomeningocele model. This study evaluated the safety of PMSC-ECM application directly onto the fetal spinal cord in preparation for a clinical trial. METHODS: Laminectomy of L5-L6 with PMSC-ECM placement directly onto the spinal cord was performed in five fetal lambs at gestational age (GA) 100-106 days. Lambs and ewes were monitored for three months following delivery. Lambs underwent magnetic resonance imaging (MRI) of the brain and spine at birth and at three months. All organs from lambs and uteri from ewes underwent histologic evaluation. Lamb spinal cords and brains and ewe placentas were evaluated for persistence of PMSCs by polymerase chain reaction for presence of human DNA. RESULTS: MRIs demonstrated no evidence of abnormal tissue growth or spinal cord tethering. Histological analysis demonstrated no evidence of abnormal tissue growth or treatment related adverse effects. No human DNA was identified in evaluated tissues. CONCLUSION: There was no evidence of abnormal tissue growth or PMSC persistence at three months following in utero application of PMSC-ECM to the spinal cord. This supports proceeding with clinical trials of PMSC-ECM for in utero myelomeningocele repair. LEVEL OF EVIDENCE: N/A TYPE OF STUDY: Basic science.

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